BEFORE THE BOARD OF APPEALS AND INTERFERENCES
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Rine et al.	Group Art Unit: 1652
Serial No. 09/165,460	Examiner: Ramirez, D.
Filed: November 3, 1998	Attorney Docket No.B96-021-3
For: *AFC1 and RCE1: Isoprenylated CAAX Processing Enzymes*	CERTIFICATE OF MAILING I hereby certify that this corr. is being deposited with the US Postal Service as First Class Mail in an envelope addressed to the Comm. for Patents, Washington, D.C. 20231 on Jan 8, 2004. Signed _____ Richard Osman

SUPPLEMENTAL BRIEF ON APPEAL

The Honorable Board of Appeals and Interferences
United States Patent and Trademark Office
Washington, D.C. 20231

Dear Honorable Board:

This is an appeal from the Dec 29, 2003 rejection of claims 31, 35, 37-39, 43 and 45-46.

REAL PARTY IN INTEREST

The real party in interest is The Regents of the University of California

RELATED APPEALS AND INTERFERENCES

Appellants are unaware of any related appeals or interferences.

STATUS OF THE CLAIMS

The Dec 29, 2003 Action indicates that claims 33-34 and 41-42 are allowable; hence, claims 31, 35, 37-39, 43 and 45-46 are subject to this appeal.

STATUS OF THE AMENDMENTS

All Amendments are believed to be properly before the Board.

SUMMARY OF THE INVENTION

A major class of peripheral membrane proteins, known as prenylated proteins, are modified by isoprenoids on a so-called $CAaa_1Aaa_2Xaa$ (CAAX) motif, wherein C is cysteine, Aaa_1 and Aaa_2 are aliphatic amino acids and Xaa is any amino acid. This tetra-peptide sequence is located at the proteins' carboxyl termini and triggers a series of modification reactions. Specification, p.1, lines 25-29.

The presence of the $CAaa_1Aaa_2Xaa$ motif sequence targets the protein for at least 3 post-translational modifications: prenylation of the cysteine amino acid, proteolytic removal of the terminal three amino acids (*i.e.*, the Aaa_1Aaa_2Xaa tripeptide) and methylesterification of the prenylated cysteine, *i.e.*, the C-terminus. Specification, p.2, lines 7-11.

It has been determined that prenylation of the CAAX motif is essential for the proper functioning of every prenylated protein that has been tested to date. However, the functional requirement of CAAX proteolysis has not been rigorously evaluated because the gene encoding the protease has been elusive. Unfortunately, elucidation of the complete yeast genome in the absence of functional information for each yeast gene is insufficient for identification of any particular gene. Although many predicted open reading frames (ORFs) have been identified, it is not known whether these ORFs encode functional mRNAs. Specification, p.2, lines 17-25.

The present disclosure describes the discovery of two families of genes which encode polypeptides that mediate the proteolytic removal of an AAX tripeptide from a prenylated CAAX protein in a cell; the families are represented by the genes *AFC1* and *RCE1* which encode the polypeptides Afc1p and Rce1p, respectively. Accordingly, the invention provides expression vectors comprising an expressed polynucleotide that encodes a CAAX protease and hybridizes under stringent conditions to a disclosed *AFC1* and *RCE1* (SEQ ID NO:1 and SEQ ID NO:2). Specifcation, p.3, lines 10-20.

The subject expression vectors are used to make Afc1p and Rce1p for disclosed protease inhibitor drugs screens, e.g. inhibiting the proteolytic removal of an AAX tripeptide from a prenylated CAAX protein in a cell. Specification, p.4, lines 10-12.

ISSUES

I. WHETHER THE EXAMINER'S REJECTION OF CLAIMS 31 and 39 UNDER 35USC103(a) IS SUSTAINABLE.

II. WHETHER THE EXAMINER'S REJECTION OF CLAIMS 35, 37-38, 43 and 45-46 UNDER 35USC103(a) IS SUSTAINABLE.

GROUPING OF THE CLAIMS

For Issue I, the subject claims shall stand together as a group.

For Issue II, the subject claims shall stand together as a group.

ARGUMENT

I. THE EXAMINER'S REJECTION OF CLAIMS 31 and 39 UNDER 35USC103(a) IS NOT SUSTAINABLE

Rose, M. et al. (GenBank Database, Accession No. Z49617) is dated Aug 11, 1997, more than a year after our Aug 7, 1996 priority date, and is hence not prior art. Hence, instead of relying on the cited art, the Examiner now identifies additional so-called supportive publications; but these additional publications could not logically have existed prior to our filing date. Consider for example, her newly provided database accession "P47154". According to the Examiner and her purported emails, the date given in the first DT line of this entry (01–FEB-1996) is the date the entry first became available for public disclosure. But P47154 makes reference to publications from 1997, 1998 and 2000. In fact, *the entry makes reference to post-filing publications of the present inventors describing the present invention.* Absent a time machine, how could an entry making reference to publications in 2000 have been publicly available in 1996?

The issue is not whether SEQ ID NOS:1 & 2 are in the prior art. Of course they are. These are the inherent sequences of natural Afc1 and Rce1 transcripts, which have long existed in nature. These sequences may also have been previously discovered by humans as part of whole-genome sequencing projects. As we have repeatedly pointed out, the entire yeast genome

was largely sequenced at the time this invention was made. Whether or not a portion of the yeast genome including AFC1 was sequenced prior to our filing date is of no consequence, because their sequences, as part of the complete genomic sequence, are merely an inherent aspect of that genome. The invention derives from identifying and characterizing two genes in isolation from the genome, and this record provides no evidence that the claimed sequences were previously isolated, characterized or in any way identified apart from gross yeast genomic sequence.

The Rose et al. database entries indicate that they were data collected by the Munich information center for protein sequences (MIPS) on behalf of the European yeast chromosome X sequencing project. Similarly, the Lye et al. entries indicate that they were data collected for the Saccharomyces cerevisiae chromosome XIII sequence project. Both studies involved sequencing entire yeast chromosomes, and the associated entries, as originally submitted to Genbank, were no more than machine-predicted open-reading frames of raw genetic sequence. These original entries anticipate or render obvious expression vectors of isolated yeast genes little more than does the source yeast chromosome.

Of course, the database entries as recovered by the Examiner include annotations identifying the genes and their functions, *as determined by the present Applicants*. Armed with this information, the entries provide motivation to create expression vectors. Without this information, the entries provide a list of every machine-construed ORF of the yeast chromosome. The Examiner identified and isolated the cited sequences from this vast, inherent set of machine-construed ORFs only by using our disclosed sequences as probes. Without the benefit of our disclosure, what would direct one skilled in the art to these particular machine-nominated ORFs, and invest the time and money required to make the claimed expression vectors?

Prior to our disclosure, there was no known ORF for Afc1. At most (and the record does not even confirm this) there was raw or machine-construed genomic sequence which included Afc1 sequence among vast genomic sequence. Here, the relevant ORFs were made know by the Applicants, and the annotations of the genomic databases were subsequently updated to reflect Applicants's disclosure. This is no evidence of record, and there will never be any evidence of record, that someone other than the Applicants provided motivation to isolate and express the natural sequence encoding Afc1.

Raw genomic sequence has long been subject to annotation from machine (computer) postulation of candidate genes, transcription factor binding sites, regulatory elements, etc. Machine reading parameters rely on simple pattern probability assessment, and may be arbitrarily adjusted to nominate arbitrarily more or fewer regions (see, e.g. Lye et al., discussed below). That is why even when entire genomes are sequenced, we get wildly different "guesstimates" of how many genes might be there, depending on which "gene-finder" program is used, and even with the same program the results vary wildly depending on what assignment stringencies are used. The human genome has been long since sequenced and subject to countless machine interpretations - yet try to find three biologists who will agree on how many ORFs there are in the human genome.

Even if the entire yeast genome sequence is prior art, and even if that whole genome was subject to computer-reading, the Examiner may not use Applicant's functional determination to go back to genomic sequence and pick out one postulated sequence among innumerable false-negatives and false-positives. If that were permissible, low stringency computer reads would anticipate or make obvious every machine-assignable function region of a sequenced genome, including candidate genes, transcription factor binding sites, regulatory elements, etc., even though most of them are biologically meaningless.

The present invention derives from identifying and characterizing two genes in isolation from the genome, and in isolation from any gross set of unsubstantiated computer predictions, and this record provides no evidence that the claimed sequences were previously isolated, characterized or in any way identified apart from gross genomic or computer sequences.

II. THE EXAMINER'S REJECTION OF CLAIMS 35, 37-38, 43 and 45-46 UNDER 35USC103(a) IS NOT SUSTAINABLE.

The art rejection applied to claims 35, 37-38, 43 and 45-46 (reciting SEQ ID NOS:3 and 4) relies on Lye, et al. (GenBank Database, Accession No. Z49260), which is also dated Aug 11, 1997, more than a year after our Aug 7, 1996 priority date, and is hence not prior art. Instead of a publication date, the Examiner appears to rely on a purported unpublished submission date. This is improper; if a database entry does not recite a publication date, it can not be relied upon

as prior art; see MPEP2128. The Action offers no evidence that the relied upon sequence was published at any time prior to Aug 11, 1997.

Here again, the issue is not whether SEQ ID NOS:1 & 2 are in the prior art. Of course they are. These are the inherent sequences of natural Afc1 and Rce1 transcripts, which have long existed in nature. These sequences may also have been previously discovered by humans as part genome sequencing projects. We previously noted that the entire yeast genome had been largely sequenced prior to the filing of our patent application, including the identification of thousands of potential ORFs which were not even known to encode functional mRNA. What Lye discloses are computer predictions of thousands of possible CDS regions. A computer is programmed to input raw genomic sequence, select all possible CDS regions over 100 codons, and then exclude those that are more than 50% overlapped by a larger predicted CDS. The authors promise that CDS regions of the initial dataset subsequently eliminated by the algorithm are nevertheless "available upon request." In addition, the disclosure provides algorithm-predicted PROSITE database matches, though the authors caution that some of these may be "fortuitous".

Lye does not disclose any gene or gene product, but the results of a first run effort to sequence the entire XIII chromosome of Saccharomyces cerevisiae. That natural yeast XIII chromosome is, of course, prior art, and Lye provides no more than an inherent property of that chromosome - its sequence. Lye discloses no more than raw genomic data weighted by a computer for thousands of possible genes and genetic elements. The Examiner uses our own disclosure to select out one of these and uses our own disclosure to provide motivation to recombine it in an expression vector. In the absence of any evidence for function, there would have been no motivation to select out one of the thousands of yeast ORFs of unknown function, isolate what may or may not be a coding sequence, and operatively join it to a promoter in an expression vector, as expressly required by our claims.

Absent a prior art suggestion that SEQ ID NO:1 or 3 encodes a protein of determined function sufficient to motivate the isolation, cloning and expression of such SEQ ID NO using techniques such as those of the cited Nozaki et al. (US Pat No 4,997,767) and Sambrook, J. et al. (Mol. Cloning, Cold Spring Harbor Press, p. 16.3-16.16) references, the claims are in compliance with 35USC103(a).

Appellants respectfully request reversal of the pending Final Action by the Board of Appeals.

We petition for and authorize charging our Deposit Account No.19-0750 all necessary extensions of time. The Commissioner is authorized to charge any fees or credit any overcharges relating to this communication to our Dep. Acct. No.19-0750 (order B96-021-3).

Respectfully submitted,
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CLAIMS ON APPEAL

31. A recombinant expression vector comprising a promoter operably linked to an expressed polynucleotide which encodes a polypeptide and hybridizes under highly stringent conditions to a nucleic acid consisting of SEQ ID NO:1, wherein said polypeptide mediates the proteolytic removal of an AAX tripeptide from a prenylated CAAX protein and said highly stringent conditions comprise hybridization and wash conditions selected to be 5° C lower than the thermal melting point (Tm) for said nucleic acid at a defined ionic strength and pH.

35. A recombinant expression vector comprising a promoter operably linked to an expressed polynucleotide which encodes a polypeptide and hybridizes under highly stringent conditions to a nucleic acid consisting of SEQ ID NO:3, wherein said polypeptide mediates the proteolytic removal of an AAX tripeptide from a prenylated CAAX protein and said highly stringent conditions comprise hybridization and wash conditions selected to be 5° C lower than the thermal melting point (Tm) for said nucleic acid at a defined ionic strength and pH.

37. A vector according to claim 35, wherein the polypeptide comprises SEQ ID NO:4.

38. A vector according to claim 35, wherein the polypeptide consists of SEQ ID NO:4.

39. A recombinant cell transduced with the vector of claim 31.

43. A recombinant cell transduced with the vector of claim 35.

45. A recombinant cell transduced with the vector of claim 37.

46. A recombinant cell transduced with the vector of claim 38.